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Sequential Measurements of Bone Lead Content by L X-Ray Fluorescence in $CaNa_2EDTA$-Treated Lead-Toxic Children

by John F. Rosen,* Morri E. Markowitz,* Polly E. Bijur,* Sarah T. Jenks,* Lucian Wielopolski,† John A. Kalef-Ezra,‡ and Daniel N. Slatkin§

With the development of L X-ray fluorescence (LXRF) to measure cortical bone lead directly, safely, rapidly, and noninvasively, the present study was undertaken to *a*) evaluate LXRF as a possible replacement for the $CaNa_2EDTA$ test; *b*) quantify lead in tibial cortical bones of mildly to moderately lead-toxic children before treatment; and *c*) quantify lead in tibial cortical bones of lead-toxic children sequentially following one to two courses of chelation therapy. The clinical research design was based upon a longitudinal assessment of 59 untreated lead-toxic children. At enrollment, if the blood lead (PbB) was 25 to 55 μg/dL and the erythrocyte protoporphyrin (EP) concentration was ≥ 35 μg/dL, LXRF measurement of tibial bone lead was carried out. One day later, each child underwent a $CaNa_2EDTA$ provocative test. If this test was positive, lead-toxic children were admitted to the hospital for 5 days of $CaNa_2EDTA$ therapy. These tests were repeated 6 weeks and 6 months after enrollment. Abatement of lead paint hazards was achieved in most apartments by the time of initial hospital discharge.

The LXRF instrument consists of a low energy X-ray generator with a silver anode, a lithium-doped silicon detector, a polarizer of incident photons, and a multichannel X-ray analyzer. Partially polarized photons are directed at the subcutaneous, medial mid-tibial cortical bone. The LXRF spectrum, measured 90° from the incident beam, reveals a peak in the 10.5 KeV region, which represents the lead Lα line. The effective dose equivalent using tissue weighting factors according to guidelines of the National Council on Radiation Protection and Measurements (1989), was 2.5 μSv. The reproducibility of replicate LXRF measurements, including the day-to-day variation of the instrument, in 26 lead-toxic children, after repositioning the instrument within 5 cm of the first LXRF measurements, was $\pm$9.2 (95% confidence limits). For an overlying tibial skin thickness of 5 mm, the minimum detection limit was 7 μg of lead/g (wet weight) at the 95% confidence interval.

Based upon a discriminant analysis, 90% of lead-toxic children were predicted correctly as being $CaNa_2EDTA$-positive or $CaNa_2EDTA$-negative. Using LXRF and PbB values to predict $CaNa_2EDTA$ outcomes, the specificity and sensitivity of these two predictors were 86 and 93%, respectively. In a significant fraction of $CaNa_2EDTA$-positive and $CaNa_2EDTA$-negative children, cortical bone lead values were similar to lead concentrations measured via bone biopsy in normal adults and lead workers in industry. By 24 weeks after enrollment, PbB, EP, and urinary lead/EDTA ratios were similar in all groups. The most dramatic decreases in net corrected photon counts by LXRF occurred in children treated twice. Mean values of cortical bone lead by LXRF at 24 weeks in all three groups of children were similar to the mean concentration in untreated $CaNa_2EDTA$-negative children at enrollment but still three to five times greater than those measured in the tibia or whole teeth of normal European children using atomic absorption. In lead-toxic children who did not qualify for treatment, additional significant accumulation of lead in bone ended once children were removed from leaded environments or returned to lead-abated apartments. These data suggest that LXRF measurements of lead in tibial cortical bone have considerable promise to replace the $CaNa_2EDTA$ test and to provide a more appropriate end point of chelation therapy than the conventional indices of PbB and EP. Moreover, markedly elevated bone lead values accumulated during early childhood may have an intergenerational impact, as maternal lead stores amassed during childhood cross the placenta and directly affect the developing fetus.

*Divisions of Pediatric Metabolism and Epidemiology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY 10467.

†Department of Radiation Oncology, State University of New York, Stony Brook, NY 11794.

‡Laboratory of Medical Physics, University of Ioannina Medical School, Ioannina, Greece.

§Medical Department, Brookhaven National Laboratory, Upton, NY 11973.

Address reprint requests to J. F. Rosen, Department of Pediatrics, Albert Einstein College of Medicine, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467.

Introduction

Lead toxicity is the most common preventable disease in preschool children today in the United States. In its 1988 report to Congress, the U.S. Public Health Service estimated that 5 million or more young children are at risk from all sources of lead, including paint and lead in food, drinking water, dust, dirt, and gasoline (*1*). This disease is likely to continue for many years because there are still about 40 million dwellings nationally with hazardous leaded paint (*1*).

Neurobehavioral (*2,3*), cognitive (*2,3*), developmental (*4,5*), and biochemical abnormalities (*6*) have been demonstrated in children with blood lead (PbB) levels below 25 μg/dL, the Centers for Disease Control's current definition of an upper limit for "normal" PbB values (*7*). Present screening and diagnostic techniques cannot identify large numbers of asymptomatic lead toxic children, many of whom may require chelation therapy. Erythrocyte protoporphyrin (EP) screening identifies only about one-half of lead-toxic children who, by definition, have elevated PbB values between 25 and 55 μg/dL (*8*). Furthermore, the residence half-time of lead in blood is short and reflects recent exposure (*9*), whereas bone lead represents a time-averaged compartment of lead with a residence time of months to years (*10*).

The decision to proceed with in-hospital chelation therapy is based upon a positive disodium calcium-edetate ($CaNa_2EDTA$) test (*11*), which is the current reference method for assessing total body lead stores (*11*). $CaNa_2EDTA$ chelates lead from extracellular fluid, thereby removing lead from hard and soft tissues, including blood (*12*). The $CaNa_2EDTA$ test requires a quantitative 8- to 24-hr urine collection, which is virtually impossible to achieve in large numbers of young children.

With the recent development of L X-ray fluorescence (LXRF) to measure cortical bone lead directly, safely, rapidly, and noninvasively (*13,14*), the present study was undertaken to *a*) evaluate LXRF as a possible replacement for the $CaNa_2EDTA$ test (*13*); *b*) quantify lead in tibial cortical bones of mildly to moderately lead-toxic children before treatment (*13*); and *c*) quantify lead in tibial cortical bones of lead-toxic children sequentially following one to two courses of chelation therapy.

Methods

The clinical research design was based upon a longitudinal assessment of 59 untreated lead-toxic children. At enrollment, PbB values were determined. If the PbB was 25 to 55 μg/dL and the EP concentration in whole blood was ≥ 35 μg/dL, LXRF measurement of tibial bone lead was carried out (Fig. 1). One day later, each child underwent a $CaNa_2EDTA$ provocative test. If this test was positive, lead-toxic children were admitted to the hospital for 5 days of $CaNa_2EDTA$ therapy at a daily dose of 1000 mg/m² given by continuous intravenous infusion. These tests were repeated 6 weeks and 6 months after enrollment. During this 6-month period, if a child qualified for a second provocative test and a second course of $CaNa_2EDTA$ treatment in the hospital, such regimens were carried out. Abatement of lead paint hazards was achieved in most apartments by the time of initial hospital discharge. In about 20% of children, alternative housing was obtained with family or friends until housing repairs were completed. By 6 to 8 weeks postenrollment, most of the major housing repairs had been completed.

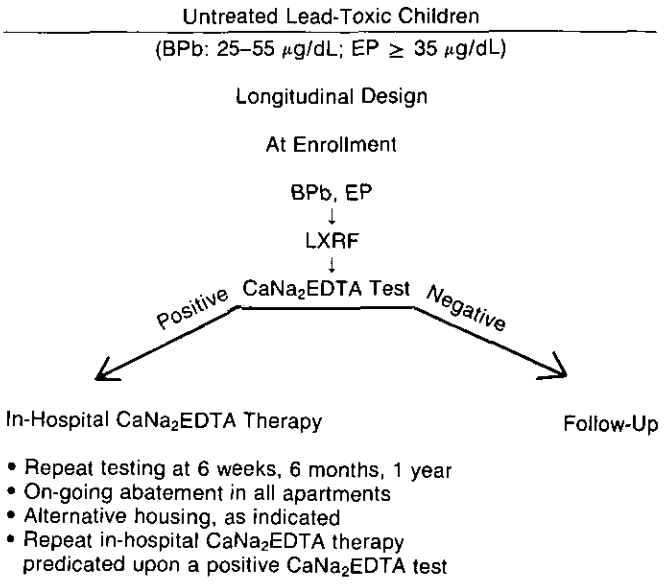

FIGURE 1. Clinical research design.

The LXRF instrument consists of a low-energy X-ray generator (Philips Electronics Model #PW1729-25) with a silver anode, a lithium-doped silicon detector, a polarizer of incident photons, and a multichannel X-ray spectrum analyzer (*13,14*). (U.S. Patent #07/158,495, assignee: Elex Analytical Technologies Corporation, Upton, NY 11973). Partially polarized photons are directed at the subcutaneous, medial midtibial cortical bone. The LXRF spectrum, measured 90° from the incident beam, reveals a peak in the 10.5 KeV region, which represents the lead Lα line. To correct for attenuation of photons by pretibial soft tissue, thickness measurements were carried out ultrasonically.

The average skin dose, deliberately limited to 1 rad over a ~4 cm² area, was delivered in 16.5 min (Table 1). The effective dose equivalent was calculated to be ≤ 2.5 microsieverts, about 1/10th to 1/20th of one dental X-ray and about 1/25th of that from one radiographic examination of the chest (*13,14*). This effective dose equivalent is < 0.1% of the average annual effective dose equivalent for an individual in the U.S. population from natural background radiation sources. Within the same population, therefore, LXRF measurements of the tibia are much less risky than those dental and pulmonary radiological examinations that

Table 1. LXRF technique: noninvasive detection of bone lead *in vivo* using polarized radiation.

X-ray generator		
High voltage	50 kVp	(Closed system;
Current	30 mA	without significant
X-ray tube anode	Ag	scattering)
Detection system		
X-ray detector	Si (Li)	
Patients		
Age	1–6 years	
Exposed area	~4 cm^2	
Imparted energy	0.1 mJ (~ 1/10–1/20 of dental X-ray)	
Effective dose equivalent	≤ 2.5 μSv (~ 1/20–1/25 of chest X-ray)	
Counting time	16.5 min	
Soft tissue (skin) thickness over the medial surface of the tibia	3–8 mm (median, 5 mm)	
Minimum detection limit	7 μg lead/g of bone with 5 mm of skin thickness	
Day-to-day instrument reproducibility	± 5.1% (95% confidence interval	
In vivo reproducibility of replicate measurements in 26 lead-toxic children	± 9.2% (95% confidence interval	

Table 2. Criteria for validation and clinical assessment of LXRF measurements in lead-toxic children (*13,14*).

Parameter	Carried out	In progress
Clinical relevance	X	
Dosimetry	X	
Closed system	X	
Parent in attendance	X	
Reproducibility of instrument	X	
Reproducibility in lead-toxic children	X	
AAS versus LXRF (surgically removed limbs)	X	
Minimum detection limit	X	
Exponential attenuation coefficient	X	
Photon count ratios		
Regression analysis		
Pregnancy–dosimetry (*15*)	X	
Further improvements in system		X
Counting time		
Lead/strontium ratios		
Minimum detection limit		

are performed routinely. Because this instrumentation was designed as an essentially closed system, a parent can be present during the LXRF examination with negligible risk from scattered radiation. The reproducibility of replicate LXRF measurements in 26 lead-toxic children, after repositioning the instrument within 5 cm of the first LXRF measurement, was ± 9.2% (95% confidence limit) (*13*).

To quantify X-ray attenuation by overlying soft tissue, the net 16.5-min photon count in the lead Lα peak from the medial aspect of the tibia of nine adult surgically amputated specimens was recorded before and after removal of epitibial soft tissue. An average effective exponential attenuation coefficient (0.45 ± 0.06 mm^{-1}, mean ± SEM) was calculated from the resultant nine photon count ratios (*13*). Similar results were obtained from regression analyses of these ratios with respect to soft tissue thickness (*14*).

The average concentration of lead in the full cross-section of tibial bone subjacent to the area of LXRF examination was measured by several flameless atomic absorption measurements of dissolved bone from each of nine amputated specimens. The correlation coefficient (r value) between LXRF measurements of bare bones and the average value of atomic absorption analyses of two full cross-sections of each specimen was 0.92 (*14*). The relative standard deviation for 18 measurements of bone lead samples by flameless atomic absorption spectroscopy (AAS) was ± 5.1% (95% confidence limits). The r value between LXRF measurements of intact limbs and AAS measurements of the bone lead samples was 0.95 (*14*). The average value of the ratio of the tibial bone lead concentration, in micrograms per gram, to the net corrected LXRF photon count, normalized to the median skin thickness of 5 mm, was 0.09 ± 0.01 (μg/g/count, mean ± SEM). For this skin thickness, the minimum detection limit was estimated to be 7 μg lead/g (wet weight) at the 95% confidence interval (*13,14*).

Based upon clinical research data already published (*13*), sequential LXRF data presented herein and a detailed study of the physics and calibration of the LXRF instrument (*14*), the validation and diagnostic applicability of this new technique have been established in lead-toxic children (Table 2). Nonetheless, further instrument improvements to decrease the counting time and enhance the minimum detection limit (MDL) below 7 μg lead/g of bone can be anticipated by modifying the geometry of the detector and using different polarizing materials (Table 2). Dosimetry measurements have also been carried out to assess the safety of LXRF measurements during pregnancy. These data indicate that one or two LXRF measurements during pregnancy is equivalent to the natural background radiation dose that the fetus is exposed to during 15 min of normal gestation (*15*).

Results

Based upon home visits and objective assessments of the quality of housing of these Bronx children, their ages, and their PbB, EP, and urinary lead-$CaNa_2EDTA$ ratios (PbU/EDTA), these lead-toxic children were representative of the majority of children attending lead-toxicity programs nationally. The $CaNa_2EDTA$-positive children had higher PbB, EP, and net corrected LXRF photon counts compared to the $CaNa_2EDTA$-negative children (Table 3) (*13*). Values for bone lead, corrected for 5 mm of overlying soft tissue in all study children, were about two times greater in $CaNa_2EDTA$-positive than in $CaNa_2EDTA$-negative children.

Correlation coefficients other than the correlation between LXRF and EP were statistically significant (Table 4) (*13*). Discriminant function analysis was car-

Table 3. PbB, EP, PbU/$CaNa_2EDTA$ values, and net corrected LXRF values in lead-toxic children (*13*).

$CaNa_2EDTA$ test result	Age, months	PbB, μg/dL	EP, μg/dL	Ratio of PbU/$CaNa_2EDTA$	Corrected LXRF values[a,b] Net photon counts	Bone Pb[c] μg Pb/g
Negative (n = 30)	33 ± 10[d]	30 ± 5[d]	89 ± 43[d]	0.39 ± 0.13[d]	159 ± 20[e]	14 ± 2[e]
Positive (n = 29)	38 ± 15*	39 ± 8*	115 ± 65†	0.95 ± 0.27†	309 ± 52*	29 ± 4*

[a] Corrected according to the day-to-day reproducibility of the instrument.
[b] Corrected to 5 mm of overlying skin thickness.
[c] Normal adult values for tibial lead are 19–27 μg Pb/g (*16,17*). Values for tibial lead in adult workers in lead industries are ≥ 30 μg Pb/g (*16,17*).
[d] Mean ± SD.
[e] Mean ± SEM.
* $p < 0.001$ versus $CaNa_2EDTA$-negative group.
† $p < 0.01$ versus $CaNa_2EDTA$-negative group.

Table 4. Statistical analyses of net corrected LXRF photon counts, PbB, EP, and $CaNa_2EDTA$ test results from 59 lead toxic children (*13*).

Pearson correlation coefficients	Analysis of tests				
	LXRF/PbB	LXRF/EP	LXRF/$CaNa_2EDTA$	PbB/$CaNa_2EDTA$	PbB/EP
r	0.388	0.200	0.472	0.701	0.499
p	< 0.003	> 0.010	< 0.001	< 0.001	< 0.001

ried out by entering corrected LXRF counts, PbB, EP, and age in a stepwise manner with the $CaNa_2EDTA$ test result as the categorical criterion variable. Based upon this analysis, 90% of lead toxic children were predicted correctly as being $CaNa_2EDTA$-positive or $CaNa_2EDTA$-negative. Neither age nor EP contributed to the power of the discriminant analysis. In a retrospective analysis of 59 similar lead-toxic children from our clinic using the indices of EP and PbB to predict $CaNa_2EDTA$ outcomes, 78% of children were correctly categorized. Hence, by including bone lead measurements by LXRF, which has a high discriminant power alone, an additional 190,000 to 650,000 lead-toxic children in the U.S. could be correctly categorized and appropriately managed medically. By using net corrected LXRF counts and PbB values to predict $CaNa_2EDTA$ outcomes, the specificity and sensitivity of these two predictors were 86 and 93%, respectively (Table 5) (*13*). In 20 and 24% of $CaNa_2EDTA$-negative and $CaNa_2EDTA$-positive children, respectively, cortical bone lead values were similar to lead concentrations measured in bone biopsies from normal adults (*16,17*). Remarkably, an additional 40% of $CaNa_2EDTA$-positive children had bone lead concentrations observed in industrially exposed adults (*16,17*).

Table 5. $CaNa_2EDTA$ test outcomes compared to predicted outcomes from a discriminant analysis using corrected LXRF photon counts and PbB values as independent variables (*13*).[a]

Actual $CaNa_2EDTA$ test results	Predicted $CaNa_2EDTA$ outcomes +	−
+	28	2
−	4	25

[a] By using net corrected LXRF photon counts and PbB to predict $CaNa_2EDTA$ test outcomes, the specificity [true negative (−) (n = 25)/true negative (−) plus false positive (+) (n = 29)] was 86% and the sensitivity [true positive (+) (n = 28)/true positive (+) plus false negative (−) (n = 30)] was 93%.

In this longitudinal study, lead-toxic children who did not qualify for treatment and other children who underwent one or two courses of $CaNa_2EDTA$ treatment were re-evaluated 6 weeks and 24 weeks postenrollment. By 24 weeks, PbB, EP, and PbU/EDTA ratios were very similar in all three groups (Figs. 2*A–C*). The most dramatic decreases in net corrected photon counts by LXRF occurred in children treated twice. In addition, there was a gradual and progressive dissociation between PbB, EP, or PbU/EDTA ratios and sequential measurements of bone lead by LXRF (Fig. 2*D*).

Mean values of cortical bone lead by LXRF at 24 weeks in all three groups of children were similar to the mean concentration in untreated $CaNa_2EDTA$-negative children at enrollment and still three to five times greater than those measured in the tibia or whole teeth of normal European children using AAS (*18–21*). In lead-toxic children who did not qualify for treatment, additional significant accumulation of lead in bone ended once children were removed from leaded environments and/or returned to lead-abated apartments (Fig. 2*D*).

Discussion

The development and clinical validation of K-line XRF instruments in industrially exposed adults (*22,23*) and the L-line XRF technique in lead-toxic chil-

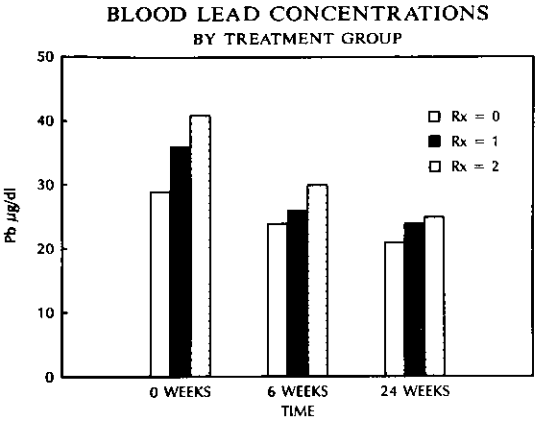

FIGURE 2. Sequential values for (*A*) PbB, (*B*) EP, (*C*) PbU/EDTA ratios, and (*D*) net corrected LXRF counts are shown in children at enrollment and 6 weeks and 6 months after enrollment. Rx = 0 indicates lead-toxic children who did not qualify for $CaNa_2$-EDTA treatment; Rx = 1 represents children treated with one in-hospital course of $CaNa_2EDTA$ after obtaining baseline values at enrollment; and Rx = 2 indicates lead-toxic children treated in the hospital with $CaNa_2EDTA$ after baseline values were obtained at enrollment and again 6 weeks postenrollment.

dren (*13,14*) open exciting and highly relevant time windows of several months to several years to assess the impact of large bone reservoirs of lead on human health. These two XRF approaches to measure lead in bone are likely to shed further understanding on the biological information obtained by measuring lead in whole blood (*6*). The LXRF technique also presents a possibility for resolving long-standing uncertainties concerning fetal exposure to lead in relation to maternal lead stores. Moreover, XRF techniques may explore epidemiological connections between hypertension (*24*) and osteoporosis (*25*).

It is clear from previous work that concentrations of lead in bone (long bones and tooth dentine) correlate closely with the presence of lead nephropathy in adults (*26*) and neurobehavioral and cognitive impairments in children (*19,21,27*) (Table 6). Furthermore, during nonsteady-state conditions (growth, pregnancy, lactation, demineralization of the skeleton), it is reasonable to expect that the metabolism of lead in bone is related more closely to skeletal remodeling and recycling rates than to chemical differences between lead and calcium.

In this study of 59 lead-toxic children, the clinical relevance and diagnostic capability of the LXRF technique have been proven. A PbB determination and LXRF measurement were predictive of the need for in-hospital chelation therapy in 90% of lead-toxic children (PbB: 25–55 µg/dL; EP ≥ 35 µg/dL). By including bone lead measurements by LXRF, several additional thousands of lead-toxic U.S. children annually could be correctly categorized and appropriately managed medically (*1*). Moreover, the capability of this new LXRF technique may be applied even more widely as considerations are given to lowering the current Centers for Disease Control's definition of an elevated PbB value as ≥ 25 µg/dL. In this regard, at mean PbB values of 33 and 38 µg/dL in $CaNa_2EDTA$-negative and $CaNa_2$-EDTA-positive children, respectively, a majority of children in both groups, by 6 years of age, have already achieved bone lead values measured in normal adults and workers in lead industries. We surmise that either an excessively narrow margin of safety or insufficient safety is provided by current U.S. guidelines, which define an elevated PbB as ≥ 25 µg/dL.

Table 6. Cortical bone lead values in children.

Reference	Subjects	Mean, ppm wet weight
Barry (*18*)	Normals	3
Winnecke (*19*)	Normals	3–5
Grandjean (*20*)	Normals	3–5
Needleman (*28*)	Lead poisoned	~31
Winnecke (*21*)	Smelter exposed	~12
Rosen et al. (*13*) (by LXRF)	Lead toxic	
	$CaNa_2EDTA$ (−)	14
	$CaNa_2EDTA$ (+)	29

Other results indicated that neither age nor EP contributed to the power of the discriminant analysis; a significant though modest correlation was observed between bone lead values by LXRF and PbB concentrations in untreated children. In children 6 months after enrollment who were untreated, treated once or treated twice (Figs. 2*A–C*), PbB, EP, and PbU/EDTA ratios returned to values currently considered to be normal. In contrast, tibial cortical bone lead concentrations remained three to five times higher than concentrations in compact tooth bone in normal European children (*18–21*) (Fig. 2*D*). These high bone lead values, at the end point of so-called successful chelation therapy, may prove to be of considerable public health significance as some of these children become women of childbearing age. Elevated bone lead values accumulated during early childhood may have an intergenerational impact, as these maternal lead stores cross the placenta and impact directly on the developing fetus.

These data indicate that LXRF measurements of lead in cortical bone may have the potential to replace the cumbersome, impractical $CaNa_2EDTA$ test. Our results also suggest that LXRF measurements of lead in bone may ultimately prove to be a more appropriate endpoint of chelation therapy than the conventional indices: PbB, EP, and PbU/EDTA. We speculate that LXRF measurements may prove to be useful predictors of the results of neurobehavioral parameters in lead-toxic children after chelation therapy.

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